Chemotherapy (CT) with radiotherapy versus CT alone for FIGO Stage IIIc endometrial cancer

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Summary

To determine optimal treatment for women with Stage IIIc endometrial carcinoma, extended-field radiotherapy (RT) plus chemotherapy (CT) was compared versus CT alone as adjuvant therapy. Twenty-nine patients with FIGO Stage IIIc endometrial cancer who underwent adjuvant treatment with 4.4 courses of CT (CAP or TC/DC) or 4.5 courses of CT (CAP or TC/DC) plus external pelvic RT (50 Gy) with paraaortic boost after surgery between 1992 and 2004 were retrospectively assessed. Fifteen patients underwent CT alone and 14 received combined treatment with CT/RT. Following treatment, the recurrence rate was 46.6% and 28.5% in the two treatment arms, respectively. There was a significant ($p < 0.05$) difference in the pelvic recurrence rate (33.3% and 7.1%, respectively). Combined treatment with RT/CT was associated with a better survival rate than CT alone (78% versus 62%, respectively). In Stage IIIc endometrial cancer, combined treatment with RT and CT reduces pelvic recurrence and improves progression-free survival and overall survival compared with CT alone.

Key words: Stage IIIc endometrial cancer; Endometrioid carcinoma; Chemotherapy; Radiotherapy; Overall survival.

Introduction

In Japan, although uterine cervical cancer is more common than uterine endometrial cancer, endometrial cancer is the fastest-increasing gynecological malignancy [1]. Possible reasons for the rising incidence of this disease include lifestyle changes among Japanese women such as diet, rates of obesity, hormonal milieu, and age at becoming pregnant. Most endometrial cancer patients are diagnosed with early-stage disease (FIGO I and II) without clinical evidence of extrauterine spreading and have relatively good prognosis with 5-year survival rates ranging from 90% in individuals with Stage I to 83% in those with Stage II disease [2]. On the other hand, patients presenting with FIGO Stage III endometrial cancer, accounting for 10-15% of all patients with this disease, reportedly have poorer prognosis with 5-year survival rates of 40-70% [3-5].

Radiotherapy (RT) alone following surgery has long been the standard of care for advanced-stage endometrial cancer in the USA. In patients with positive paraaortic lymph nodes at the time of initial surgical treatment, RT following surgery is curative in only 40% of cases [6]. In Japan, on the other hand, the standard approach for patients with advanced endometrial cancer is postoperative chemotherapy (CT). This strategy seems justifiable in light of a recent randomized study that showed a survival advantage favoring adjuvant CT compared with adjuvant RT in advanced patients [6]. Hence although management of patients with Stage I-II disease is relatively straightforward, adjuvant therapy in Stage III and IV disease is not well defined. Several studies have investigated the efficacy of CT [7-10], RT [11-13], and combination treatment with RT/CT [5, 14, 15] with varying results.

In advanced endometrial cancer, we consider that not only local control using RT but also systemic control using CT is needed. The purpose of this study was to determine the toxicity of cisplatin- or carboplatin-based CT followed by standard whole-pelvic RT and to evaluate the long-term survival rate of this strategy compared with CT alone in Stage IIIc endometrial cancer patients.

Patients and Methods

Patients

This report summarizes outcomes in patients with Stage IIIc endometrial cancer of all histological subtypes who underwent treatment at Sapporo Medical University Hospital between 1992 and 2004. Patients were required to have pathologically confirmed primary endometrial cancer with surgical Stage IIIc disease. Operative reports were reviewed for procedures performed and surgical findings, and pathology reports were reviewed for tumor grade, depth of invasion, number of lymph nodes removed, number of positive nodes, and presence of positive cytology, adnexa, and uterine serosa. Kaplan-Meier survival curves were constructed and differences in survival compared by the log-rank test. Written informed consent for data manipulation/reappraisal such as in this retrospective reanalysis was obtained from all patients prior to study entry in accordance with institutional regulations. This study was conducted in accordance with the principles of the Helsinki Declaration of 1975 as revised in 2000.

Management strategy

At our hospital, following surgery patients with Stage IIIc were managed by one of two clinical teams; one team selected CT alone whereas the other gave CT followed by RT.

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Surgical procedures

None of the patients received preoperative RT or CT. All patients underwent radical hysterectomy, bilateral salpingo-oophorectomy, pelvic washings, and had removal of pelvic lymph nodes (PLN) and paraaortic lymph node (PALN) dissection. Omentectomy was not necessarily required but sometimes sections of the omentum with gross metastases were excised.

Chemotherapy

Patients with GOG performance status 0-2 underwent CT within three weeks postoperatively. Other eligibility requirements included adequate bone marrow function with absolute neutrophil count > 2500/mm^3 and platelets > 100,000/mm^3. Patients were excluded if they had congestive heart failure, cardiac ejection fraction < 45%, history of recent MI within six months prior to surgery, SGOT > 2 × upper limit of normal (ULN), bilirubin > 1.0 × ULN, or creatinine > 2.0 mg/dl. Patients with concurrent invasive malignancy, active psychiatric or mental illness that made informed consent or careful clinical follow-up unlikely, or sensitivity to Escherichia coli-derived drug preparations were excluded. Patients were treated with three to five cycles of cisplatin, cyclophosphamide, and aclarubicin (CAP); paclitaxel and carboplatin (TC); or docetaxel and carboplatin (DC); combination CT schema and doses of each regimen are detailed in Figure 1. Complete blood counts were performed twice weekly while patients were on G-CSF, otherwise once weekly.

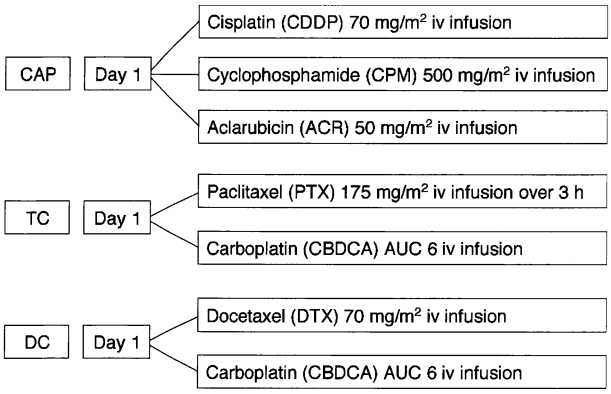

Figure 1. — Chemotherapy schema. CAP, cyclophosphamide + adriamycin + platina; TC, paclitaxel + CBDCA; DC, docetaxel + CBDCA.

Radiotherapy

Postoperatively, eligible patients received external whole pelvic RT plus paraaortic RT (EFRT). Patients were to be treated with two pairs of parallel opposed fields (open-field technique) to the whole pelvis and paraaortic nodes. Radiotherapy was given in five fractions/week (daily dose, 2 Gy) for five weeks. The pelvic field extended from the L5-S1 interspace superiorly to the bottom of the obturator foramina inferiorly and the lateral margins were 1.5 cm lateral to the medial rim of the ilium. The paraaortic field extended to the top of T12 and kidney blocks were used.

Results

Patients

Between 1992 and 2004, 312 patients received surgical therapy for endometrial cancer in Sapporo Medical University Hospital, among whom 29 eligible patients with FIGO Stage IIIc disease were retrospectively identified. Among these 29 patients, histologically 22 had endometrioid carcinoma, three adenosquamous carcinoma, two serous adenocarcinoma, one carcinosarcoma, and one mixed type with endometrioid and serous adenocarcinoma. Average age of the patients was 59.9 (range, 24-79) years. Three of the 29 patients had a history of breast cancer, 11 had hypertension, and three diabetes mellitus (Table 1).

Table 1. — *Clinical characteristics of FIGO Stage IIIc endometrial cancer.*

Parameter	Value
No. of patients	29
Performance status (ECOG)	
0	27
1	2
≥ 2	0
Median (range) age at diagnosis, years	59.9 (24-79)
Median (range) parity, n	3 (0-7)
Median (range) weight, kg	57.8 (34-74)
Prior history of breast cancer, n	3
Prior history of hypertension, n	11
Prior history of DM, n	3
Histology	
Endometrioid	22
G1	2
G2	4
G3	16
Adenosquamous	3
Serous papillary	2
Carcinosarcoma	1
Mixed	1

Following recovery from surgery (2-4 weeks), 14 patients with FIGO Stage IIIc underwent both RT and CT, and 15 patients with FIGO Stage IIIc received CT alone. In the RT/CT group, nine patients received a mean of 4.5 (range, 3-5) cycles of CAP and five received 5 cycles of TC (DC) therapy. All RT/CT patients underwent external whole pelvic RT with the goal of delivering 50 Gy and a boost to the paraaortic nodes. In the CT group, nine patients received a mean of 4.4 (range, 4-7) cycles of CAP and six patients received 4.4 (range, 3-6) cycles of TC (DC) therapy (Table 2).

Table 2. — *Summary of interventions in CT and RT/CT groups.*

Modality	CT group (n = 15)	RT/CT group (n = 14)
Surgery		
RT+BSO+PLN+PAN	15	14
Chemotherapy		
TC (DC)	6	5
CAP	9	9
Radiotherapy		
EFRT 50 Gy	–	14

RT, Radical hysterectomy; BSO, Bilateral salpingo-oophorectomy; PLN, Pelvic lymphadenectomy; PALN, Paraaortic lymphadenectomy; EFRT, extended-field RT (whole-pelvic RT plus paraaortic RT).

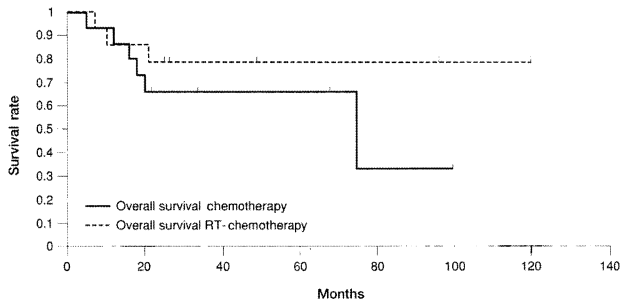

Figure 2. — Overall survival rate in patients with FIGO Stage IIIc endometrial cancer. *p = 0.0852.

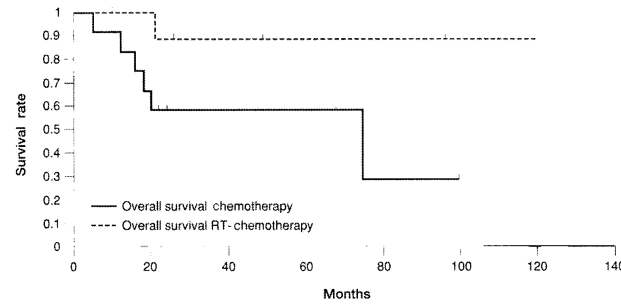

Figure 3. — Overall survival rate in patients with FIGO Stage IIIc endometrioid carcinoma type. *p = 0.0165.

Among patients who received RT/CT, five had cervical extension, four stromal extension, and two invasion of uterine serosa. Among patients who underwent CT alone four had cervical extension, three stromal extension, and two invasion of uterine serosa (Table 3).

All patients underwent PLN and PALN. In the group who received RT/CT, all patients were lymph node positive and six of 14 patients were positive in both pelvic and paraaortic lymph nodes. In the CT alone group, all patients were also lymph node positive and four of 15 patients were positive in both pelvic and paraaortic lymph nodes (Table 3).

Patterns of failure

Table 4 summarizes the risk of recurrence in each group. Even though the total number of patients was small, it was clearly seen that in those who received RT plus CT, relapse in the pelvic area was better controlled compared with in those who received CT alone.

In the FIGO Stage IIIc patients, total local or distant recurrence rates were 4/14 (28.5%) in those treated with RT plus CT and 7/15 (46.6%) in those receiving CT alone. Of note, patients treated with RT plus CT had lower abdominal relapse (1/14, 7.1%) than patients treated with CT alone (5/15, 33.3%).

The risk of distant recurrence was similar in patients treated with RT plus CT (3/14; 21.4%) and those who received CT alone (2/15; 13.3%).

Table 3. — *Pathologic distribution of disease in patients with Stage IIIc endometrial cancer.*

	CT group (n = 15)	RT/CT group (n = 14)
Cytology positive	3	3
Cervical extension	4	5
Cervical stromal invasion	3	4
Uterine serosal extension	2	2
Adnexal involvement	1	2
Depth of invasion		
Endometrium only	0	0
Inner 1/3	0	0
Medial 1/3	3	1
Outer 1/3	10	11
Serosal extension	2	2
Nodal involvement		
Pelvic/paraaortic lymph nodes (+)	4	6
Pelvic lymph nodes (+)	9	5
Paraaortic lymph nodes (+)	2	3
Lymph nodes (–)	0	0
> 2 positive pelvic lymph nodes	8	10
One side positive	4	3
Bilateral positive	4	7

Table 4. — *Patterns of failure in patients receiving postoperative adjuvant CT or RT/CT.*

	First site of recurrence		
	Pelvic	Extrapelvic	No recurrence
CT group (n = 15)	5 (33.3%)	2 (13.3%)	8 (53.4%)
RT/CT group (n = 14)	1 (7.1%)	3 (21.4%)	10 (71.5%)

Progression-free survival

At a mean follow-up of 62 (range, 6.7-120) months, 5-year Kaplan-Meier progression-free survival (PFS) rates associated with RT plus CT and CT alone were 78% and 62%, respectively (Figure 2). Among endometrioid histology patients at FIGO Stage IIIc, 5-year PFS was 88% in those who received RT plus CT and 58% in those who underwent CT (Figure 3).

Toxicity

Combined treatment was well tolerated in the majority of patients. Five of 14 (35.7%) patients had grade four leukopenia at nadir, but no febrile neutropenia was recorded and no patient required hospitalization for hematologic toxicity. Grade 3 diarrhea was reported in four of 14 patients (28.6%), but no patient refused treatment because of diarrhea (Table 5).

Table 5. — *Adverse effects (grades 3-4) of CT with or without RT.*

	RT/CT group	CT group
Leucopenia	9	7
Neutropenia	11	11
Thrombocytopenia	2	2
Anemia	3	1
Diarrhea	4	–
Other GI	2	2
Cardiotoxicity	1	–
Neurotoxicity	–	–
Renal dysfunction	–	–
Liver failure	–	–

In the CT alone group, four of 15 (26.7%) patients had grade 4 leukopenia at nadir, but no patient reported diarrhea.

In general, both combined therapy and CT alone were well tolerated and toxicities observed during treatments were comparable to those usually reported in patients who receive these treatment regimens.

Conclusions

In the USA, pelvic and whole abdominal RT is generally used as postsurgical strategy for FIGO Stage IIIc patients, but even so advanced endometrial cancer patients have a poor prognosis. Adjuvant RT appears to reduce the incidence of pelvic relapses but does not improve long-term survival [16]. Chambers *et al.* [17] reported that > 90% of relapse observed in patients treated with adjuvant RT developed out of the irradiation field. Studies of adjuvant CT have not shown that this strategy increases long-term survival [18]. Morrow *et al.* [19] reported that CT after surgery and radiation did not affect disease-free survival (DFS) compared with surgery and RT. Onda *et al.* [20] reported that RT combined with CT for endometrial cancer FIGO Stage IIIc gave a 5-year overall survival (OS) rate of 84%, and Bruzzone *et al.* [5] showed that combined therapy enhanced PFS to 30% at nine years and OS to 53% at nine years in FIGO Stage III-IV endometrial cancer patients.

Our results suggest that relapse in patients treated with adjuvant RT plus CT did not develop in the pelvic field, although there was not a significant difference in relapse rate between combined therapy and CT alone out of the irradiation field for Stage IIIc patients. On the whole, successful control in the pelvic area contributed to the low observed rate of recurrence in CT/RT patients. PFS among patients with Stage IIIc disease was 78% with RT/CT and 62% with CT alone. Especially, in patients with endometrioid-type uterine corpus cancer the PFS with RT/CT was markedly better than in the CT group. On the whole, however, among Stage IIIc patients RT combined with CT was associated with longer PFS than CT alone.

Randall *et al.* [7] reported that adjuvant CT with doxorubicin and cisplatin resulted in 5-year survival of 55% whereas the rate in patients who underwent adjuvant whole-pelvic RT was 42%. In our study, combined RT/CT after surgery reduced relapse rate in the pelvic area. Furthermore, overall toxicity did not stop the treatment.

Frigerio *et al.* [14] reported good tolerability of weekly paclitaxel with concurrent RT for patients with high-risk endometrial cancer, and Hoskins *et al.* [21] also suggested that weekly TC therapy (every 4 weeks) with RT reduced general toxicities compared with TC alone.

There is no general consensus among oncologists regarding irradiation strategies. At different centers, patients might undergo whole abdominal RT (WART), whole-pelvic RT (WPRT), or WPRT plus paraaortic RT (PART) (extended-field RT; EFRT) [22-24]. However, in 2001 Mundt *et al.* [11] reviewed failure patterns among their patients and found that the optimal adjuvant RT volume was EFRT even in women with negative PALN sampling. Our results support this contention because in three patients with positive PALN who underwent EFRT no recurrence was observed. What is interesting is that the CT/RT group had a higher percentage of women with bilateral pelvic lymph node involvement yet had a lower pelvic relapse rate. Although the sample size was small and this was a retrospective analysis, we interpret the results as indicative of a strong possibility of suppressing the cancer growth by comcomitant CT/RT.

For patients with Stage IIIc endometrial cancer, combined CT/RT seems an effective treatment strategy. The observed 5-year survival rate of 78% in these patients with a generally poor prognosis represents an encouraging result. Advances of combined therapeutic strategies could be the way to further improve outcome in these patients. We consider that combined RT/CT has the potential to control local recurrence and improves long-term survival.

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